568. *Conformational Anomalies in Some Triterpenoid Bromo-ketones.*

By D. H. R. Barton, D. A. Lewis, and J. F. McGhie.

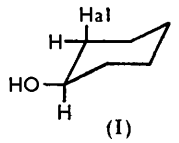
Monobromination of lanost-8-en-3-one affords 2α- (95%) and 2β-bromolanost-8-en-3-one (5%). The configurations of these compounds have been established by study of the derived bromohydrins obtained by reduction with sodium borohydride. Both bromo-ketones have ultraviolet and infrared spectra indicative of equatorial bromine. This can be explained by postulating a preferred boat conformation for ring A in 2β-bromolanost-8-en-3-one.

Monobromination of lanostan-3-one affords only 2α-bromolanostan-3-one. The 2β-bromo-analogue has been prepared by an indirect method. Both monobromo-ketones have equatorial bromine as judged by their absorption spectra and, again, a preferred boat conformation must be postulated for the 2β-bromo-compound.

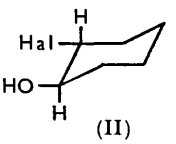
Anomalies in the opening of 2β : 3β-epoxy-derivatives of lanost-8-ene and lanostane are discussed and rationalised in conformational terms.

The reliable and effective method for the elucidation of halogen configuration in steroidal α-bromo-ketones is chemical and relies upon the following argument.[1] α-Bromo-ketones are reduced by sodium borohydride to bromohydrins. On treatment with alkali *cis*-bromohydrins afford ketones, whilst *trans*-bromohydrins give epoxides.[2] If therefore a bromo-ketone is reduced to a bromohydrin and the latter is (*a*) treated with alkali and (*b*) reductively dehalogenated to the parent alcohol of known configuration, it becomes simple to deduce the configuration of the bromine atom.

In principle, one would expect the reaction of alkali with *cyclo*hexanic halogenohydrins to be subject to conformational control in that the four centres of importance in the reaction should lie in one plane for maximal reaction rate.[3] This means that for epoxide formation hydroxyl and halogen, and for ketone formation the hydrogen and halogen, should preferably both be axial. In substituted *cyclo*hexanes having the usual chair conformation, four types of 1 : 2-halogenohydrins can therefore be distinguished (I—IV). Substances containing the systems (I) and (III) should react rapidly with alkali to give ketone and epoxide respectively : those containing the systems (II) and (IV) should react slowly, to give (epimeric) epoxide and ketone respectively. The data summarised in Table 1 for some steroidal halogenohydrins of defined conformation support these generalisations.[4]



(I)



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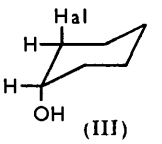
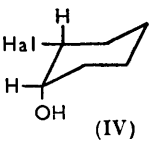


(III)



(IV)

The conformations of α-halogeno*cyclo*hexanones and, by implication, their configurations can also be determined by physical methods. Thus equatorial α-halogeno*cyclo*hexanones show a shift of the infrared carbonyl frequency to higher wave numbers relative to the frequency for the parent ketones : the axial analogues in contrast show little displacement.[5] The reverse situation holds for the ultraviolet absorption spectra of α-halogeno*cyclo*hexanones, the axial compounds showing a shift in wave length and

[1] Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 1700; Fieser and Dominguez, *ibid.*, p. 1704; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837.
[2] Bartlett, *ibid.*, 1935, **57**, 224.
[3] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44, and references there cited.
[4] See Barton, *Experientia*, Suppl. II, 1955, 121.
[5] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

intensity of maximal absorption, the equatorial compounds approximating in behaviour to the parent ketone.[6]

The conformations of *cyclo*hexanic halogenohydrins can also be explored by an infrared method. Thus, for example, axial bromine confers one or more strong bands in the 500—600 cm.$^{-1}$ region, whilst equatorial bromine gives one or more bands in the 700 cm.$^{-1}$ region.[7]

All these techniques have proved of value in the study of various bromo-ketones derived from lanosterol.

TABLE 1.

Halogenohydrin	Refs.	Conformation of halogen eliminated	Conformation of OH or H eliminated	Time (min.) required for % reaction under standard conditions (see Experimental) 5%	40%	70%
2α-Chlorocholestan-3β-ol ...	*a*	e (Cl)	e (OH)	4560	—	—
2α-Bromocholestan-3β-ol ...	*b, c*	e (Br)	e (OH)	—	600	1440
2α-Bromolanost-8-en-3β-ol ...	*d*	e (Br)	e (OH)	—	120	3000
2α-Bromolanostan-3β-ol	*d*	e (Br)	e (OH)	—	1000	4500
2β-Chlorocholestan-3α-ol ...	*e*	a (Cl)	a (OH)	—	0·8	2·4
2β-Bromocholestan-3α-ol ...	*e*	a (Br)	a (OH)	—	0·25	0·6
2β-Bromolanostan-3α-ol	*d*	a (Br)	a (OH)	—	4	8
2β-Bromolanost-8-en-3β-ol ...	*d*	a (Br)	a (H)	—	3	10
2β-Bromolanostan-3β-ol	*d*	a (Br)	a (H)	3	10	40
3α-Chlorocholestan-2β-ol ...	*e*	a (Cl)	a (OH)	—	1·2	2·8
3α-Bromocholestan-2β-ol ...	*e*	a (Br)	a (OH)	—	0·2	0·4

[a] Beereboom, Djerassi, Ginsburg, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500. [b] Fieser and Huang, *ibid.*, p. 4837. [c] Corey, *ibid.*, p. 4833. [d] This paper. [e] Alt and Barton, *J.*, 1954, 4284.

Treatment of lanost-8-en-3-one (V) with 1 mol. of bromine gave a mixture of monobromo-ketones. The major product was characterised as the expected 2α-bromolanost-8-en-3-one (VI) on the following evidence. Reduction with zinc gave back the parent ketone. Heating with collidine gave lanosta-1 : 8-dien-3-one. Reduction with sodium borohydride afforded 2α-bromolanost-8-en-3β-ol (VII), reconverted into the bromo-ketone by chromium trioxide. Treatment with alkali afforded 2β : 3β-epoxylanost-8-ene (VIII). Reduction of the bromohydrin (VII) with zinc gave lanost-8-en-3β-ol (IX). These facts (cf. above) establish the configuration of the bromohydrin (VII) and hence of the parent bromo-ketone (VI). The expected conformation (X) of the bromohydrin (VII) is confirmed by an equatorial-bromine infrared band at 724 cm.$^{-1}$ (band at 730 cm.$^{-1}$ in derived acetate) and by the slow reaction (see Table 1) with alkali. The conformation of the 2α-bromolanost-8-en-3-one is also as expected (XI; equatorial bromine), as shown by the data summarised in Table 2.

The minor product of the bromination gave with sodium iodide a monoiodo-ketone. This compound was also obtained from 2α-bromolanost-8-en-3-one with the same reagent and is regarded as 2α-iodolanost-8-en-3-one. The minor bromination product must therefore be the stereoisomer of the 2α-bromo-ketone, *i.e.*, 2β-bromolanost-8-en-3-one (XII). The following evidence confirmed this. Reduction with zinc gave back lanost-8-en-3-one. Treatment with sodium borohydride furnished a bromohydrin, which was reduced by zinc to lanost-8-en-3β-ol (IX) and gave lanost-8-en-3-one (V) with alkali. The bromohydrin must therefore be 2β-bromolanost-8-en-3β-ol (XIII), and the parent ketone must be the 2β-compound (XII) as already formulated. The conformation of (XIII) must be the expected one (XIV) since the compound showed an infrared band at 515 cm.$^{-1}$ indicative of axial bromine (band at 603 cm.$^{-1}$ in the derived acetate) and reacted rapidly with alkali (diaxial elimination : see Table 1). However, the bromo-ketone (XII) clearly did *not* have the expected conformation (XV), since the spectroscopic data (Table 2) clearly indicated equatorial, not axial, bromine. The only rational explanation is that

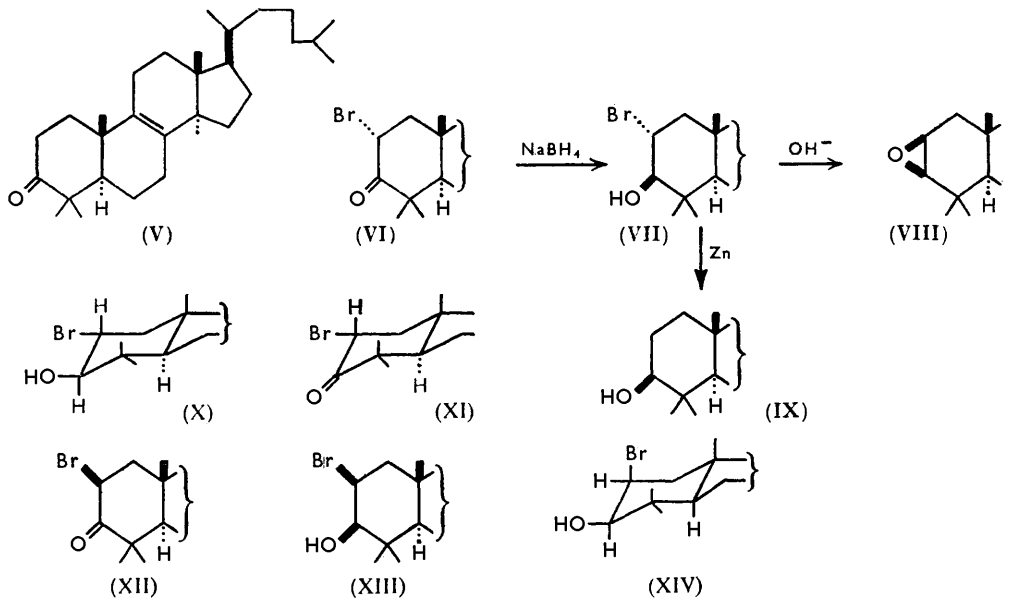
[6] Cookson, *J.*, 1954, 282.
[7] Barton, Page, and Shoppee, *J.*, 1956, 331.

ring A of the bromo-ketone (XII) assumes a boat (XVI) rather than a chair (XV) conformation. One can understand some of the factors which dictate this preference. In the

TABLE 2.

Ketone	$\lambda_{max.}$ (mμ)	$\nu_{max.}$ (cm.$^{-1}$)	Shift on substitution, and derived halogen conformation	
			$\Delta\lambda_{max.}$	$\Delta\nu_{max.}$
Lanost-8-en-3-one	288	1703	—	—
2α-Bromolanost-8-en-3-one	291	1728	+3 (e)	+25 (e)
2β-Bromolanost-8-en-3-one	282	1734	−6 (e)	+31 (e)
Lanostan-3-one	294	1704	—	—
2α-Bromolanostan-3-one	289	1726	−5 (e)	+22 (e)
2β-Bromolanostan-3-one	285	1732	−9 (e)	+28 (e)

chair conformation (XV), there are powerful 1 : 3-interactions between the axial bromine and the two axial 4- and the 10-methyl group. These repulsive interactions are avoided



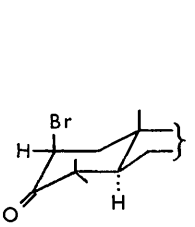
in the boat conformation (XVI).[8] Now the boat conformation of *cyclo*hexane is strongly destabilised by 1 : 4-interaction of axial hydrogen atoms,[9] but when the appropriate carbon atom is made trigonal by a ketone group this interaction is removed. Such a situation pertains in conformations (XV) and (XVI). This factor also helps to explain why the derived bromohydrin assumes the chair conformation (XIV). Clearly the 1 : 4-interaction of the 3β-hydroxyl and the 10β-methyl group in the boat conformation corresponding to (XIV) would be prohibitive. The two bromo-ketones (VI) and (XII) could be equilibrated by using hydrogen bromide as catalyst, the equilibrium at room temperature being 95% on the side of the 2α-compound. One can calculate, therefore, that the free-energy difference between conformations (XI) and (XVI) is approximately 1·8 kcal. mole^{-1}.

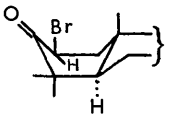
So far as we are aware, this is one of the first occasions on which a *cyclo*hexane ring which can be formulated as either a chair or a boat form actually exists in the latter. The claims made have therefore been confirmed by experiments on lanostan-3-one (XVII), as follows.

[8] Cf. Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325; Fieser and Dominguez, ref. 1; Jones, *J. Amer. Chem. Soc.*, 1953, **75**, 4839.

[9] Barton, *J.*, 1948, 340; Angyal and Mills, *Rev. Pure Appl. Chem.*, 1952, **2**, 185; Shoppee, *Chem. and Ind.*, 1952, 86; Beckett and Mulley, *J.*, 1955, 4159.

Lanostan-3-one with an excess of bromine gave the 2 : 2-dibromo-compound (XVIII). With 1 mol. of bromine, on the other hand, it afforded a single monobromo-derivative. The latter was also obtained by conversion of lanostan-3-one into its enol acetate (XIX)


(XV)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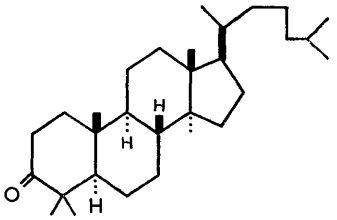
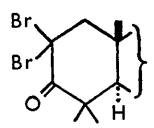

(XVII)

by excess of *iso*propenyl acetate followed by reaction with bromine. This monobromolanostan-3-one was shown to be the 2α-derivative [as (VI)] by the following evidence. Reduction with zinc gave back lanostanone; treatment with collidine gave lanost-1-en-3-one. Refluxing with sodium iodide afforded an iodo-ketone regarded as 2α-iodolanostanone. Reduction with sodium borohydride furnished a bromohydrin, which gave lanostan-3β-ol [as (IX)] on reduction with zinc and afforded 2β : 3β-epoxylanostane [as (VIII)] on treatment with alkali. The bromohydrin must, therefore, be 2α-bromolanostan-3β-ol [as (VII)], and the parent bromo-ketone 2α-bromolanostan-3-one [as (VI)]. The conformation [as (X)] of the bromohydrin was established by its slow rate of reaction with alkali (see Table 1) and by its equatorial-bromine absorption at 715 cm.$^{-1}$ (band at 720 cm.$^{-1}$ in the derived acetate). The conformation of 2α-bromolanostanone was established as that expected [as (XI)] from the spectral properties (see Table 2).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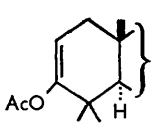
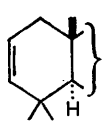

(XIX)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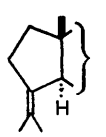
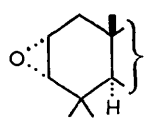

(XXI)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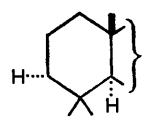
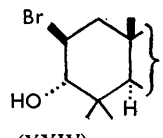

(XXIII)

Since there was no indication that 2β-bromolanostanone [as (XII)] was formed in the bromination an indirect preparation was adopted. Lanost-2-ene (XX) was obtained by pyrolysis of lanostan-3β-yl benzoate or by the action of zinc on 2α-bromolanostan-3β-yl acetate. The hydrocarbon was also prepared, in admixture with 3-*iso*propylidene-A-norlanostane (XXI), by dehydration of lanostanol with phosphorus oxychloride. Treatment of lanost-2-ene with perbenzoic acid gave 2α : 3α-epoxylanostane (XXII). The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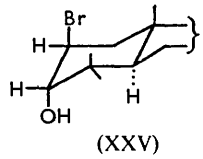
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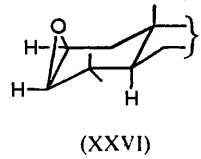
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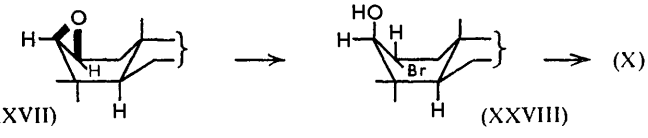
(XXVII) (XXVIII) (X)

configuration of this epoxide was confirmed by reduction with lithium aluminium hydride to lanostan-3α-ol (XXIII), which on oxidation gave lanostan-3-one. On treatment with hydrobromic acid the oxide afforded 2β-bromolanostan-3α-ol (XXIV), which was oxidised by chromic acid to the desired 2β-bromolanostan-3-one [as (XII)]. Reduction of the last

compound with sodium borohydride furnished 2β-bromolanostan-3β-ol [as (XIII)]. With alkali 2β-bromolanostan-3α-ol (XXIV) gave the parent epoxide (XXII) in a rapid reaction (Table 2). This reaction, as well as the axial bromine band at 636 cm.$^{-1}$ (bands at 603 and 630 cm.$^{-1}$ in the derived acetate), establish the preferred conformation as the expected (XXV). Reaction of 2β-bromolanostan-3β-ol with alkali rapidly (Table 2) gave lanostan-3-one. This confirmed the expected conformation [as (XIV)], as did the infrared axial-bromine band at 521 cm.$^{-1}$.

The conformation of 2β-bromolanostan-3-one was also found to be the boat [as (XVI)], not the chair [as (XV)], form. This is established by the equatorial-bromine bands in the ultraviolet and infrared spectra (see Table 2). Equilibration with hydrogen bromide converted 2β-bromolanostan-3-one quantitatively into the 2α-isomer, the accuracy of the rotational method employed being such that more than 1% of the 2β-compound would have been detected. The free-energy difference between the two bromo-ketones is, therefore, at least 2·8 kcal. mole^{-1}. Thus the effect of the 8 : 9-ethylenic linkage in ring B is conformationally transmitted [4, 10] to a significant extent into ring A to alter the position of the bromo-ketone equilibrium. The failure to isolate a second bromo-ketone on bromination of lanostan-3-one is therefore understandable.

A further conformational anomaly was found in the reactions of the 2β : 3β-epoxides of lanost-8-ene and lanostane. Diaxial opening of these epoxides should furnish 2β-hydroxy-3α-substituted derivatives as, for example, in the opening of 2β : 3β-epoxycholestane.[11] In fact, reduction with lithium aluminium hydride gave in both cases the equatorial 3β-alcohol, whilst reaction with hydrobromic acid furnished the corresponding diequatorial 2α-bromo-3β-hydroxy-compounds from which the epoxides had originally been prepared. A simple explanation for these results would be if the conformations of the 2β : 3β-epoxides were based, not on distorted chairs (XXVI), but on distorted boats (XXVII). Diaxial opening of the latter would afford the boat conformations (XXVIII) of the 2α-bromo-3β-hydroxy-compounds, which would, of course, at once be inverted to the chair conformations (X). Another example of abnormal epoxide opening)een given by Wendler, Taub, Dobriner, and Fukushima : [12] this was considered to b tronic in origin, but the anomaly may be of conformational nature as suggested for the 2β : 3β-epoxides above.

Experimental

Rotations are for $CHCl_3$ solutions and 4 dm. tubes; ultraviolet absorption spectra were taken in EtOH on the Unicam S.P. 500 Spectrophotometer. Infrared spectra were taken in CS_2 solution. We are indebted to Dr. J. E. Page (Glaxo Laboratories Ltd.) and to Dr. G. Eglinton and his associates (Glasgow) for taking the spectra and for helpful discussions. Infrared spectra were also determined by Miss E. M. Tanner of Parke, Davis and Co. Ltd., through the kindness of Dr. R. E. Bowman. Activated alumina was Peter Spence's Grade H, 100—200 mesh. Light petroleum refers to the fraction of boiling range 60—80°, unless stated to the contrary.

Monobromination of Lanost-8-en-3-one.—Lanost-8-en-3-one (4·26 g.) in glacial acetic acid (70 ml.; slight warming to effect solution) was treated at 20° during 5 min. (efficient stirring) with bromine (0·55 ml.) in the same solvent (30 ml.). The solution was then set aside at about 14° for 1½ hr. and seeded with 2α-bromolanost-8-en-3-one (see below). This gave needles (3·2 g.), m. p. 128—129°. Crystallisation from ethanol furnished *2α-bromolanost-8-en-3-one* (2·2 g.), needles, m. p. 138—139°, $[\alpha]_D$ +19° (*c* 0·95), $\lambda_{max.}$ 291 mμ (log ε 1·73) (Found : C, 71·7; H, 9·8; Br, 15·3. $C_{30}H_{49}OBr$ requires C, 71·3; H, 9·8; Br, 15·8%). The acetic acid mother-liquors, left overnight at about 14°, gave material (470 mg.) which, on crystallisation from ethanol, afforded *2β-bromolanost-8-en-3-one* (350 mg.), plates, m. p. 167—168°, $[\alpha]_D$ +170° (*c* 1·39), $\lambda_{max.}$ 282 mμ (log ε 1·77) (Found : C, 71·0; H, 9·5; Br, 15·9%).

In other runs the separation of the two compounds was not always so complete. The mixture was usually separated by brief treatment with warm ethyl acetate. The less soluble

[10] Barton, Head, and May, *J.*, 1957, 935.
[11] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 279; Alt and Barton, *J.*, 1954, 4284.
[12] Wendler, Taub, Dobriner, and Fukushima, *J. Amer. Chem. Soc.*, 1956, **78**, 5027.

2β-bromolanost-8-en-3-one was left on decantation, whilst the more soluble 2α-isomer was recovered from the solution.

Both bromo-ketones were debrominated by the following method. The bromo-ketone (100 ml.) in glacial acetic acid (15 ml.) was treated with " AnalaR " zinc dust (4 × 200 mg.) under reflux during 2 hr. Crystallisation from ethanol afforded in both cases lanost-8-en-3-one, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +77° (*c* 0·72) and +77° (*c* 0·83) for the 2α- and 2β-isomer respectively}.

Equilibration of 2α- *and* 2β-*Bromolanost-8-en-3-one.*—The bromo-ketones (52 mg.) in chloroform (10 ml.) with addition of hydrogen bromide (*d* 1·5) in acetic acid (1·0 ml.) were left in a 2 dm. polarimeter tube at room temperature. The initial readings were $[\alpha]_D$ +18° and +170°, and the final readings (three days) +26° and +25° for the 2α- and 2β-bromo-ketone respectively. Recovery of material gave in each case needles, m. p. and mixed m. p. 124—129°.

2α-*Bromolanost-8-en-3β-ol and its Derivatives.*—2α-Bromolanost-8-en-3-one (2·0 g.) in benzene–absolute methanol (2 : 7; 90 ml.) was treated with sodium borohydride (1·0 g.) at 19° for 2 hr. Crystallisation from methylene dichloride–methanol gave 2α-*bromolanost-8-en-3β-ol* (1·6 g.), needles, m. p. 136—137° (decomp.), $[\alpha]_D$ +26° (*c* 0·73), max. at 3640 and 1038 cm.$^{-1}$ (equatorial OH) (Found: C, 71·2; H, 9·6; Br, 16·0. $C_{30}H_{51}OBr$ requires C, 71·0; H, 10·1; Br, 15·7%). Treatment with pyridine–acetic anhydride overnight at room temperature afforded the *acetate*, needles (from methylene dichloride–methanol), m. p. 148—149°, $[\alpha]_D$ +16° (*c* 1·06), max. at 1745 and 1230 cm.$^{-1}$ (acetate) (Found: C, 70·0; H, 9·2; Br, 14·65. $C_{32}H_{53}O_2Br$ requires C, 69·9; H, 9·7; Br, 14·5%).

When 2α-bromolanost-8-en-3β-ol (2·6 g.) was treated under reflux with 5% absolute-ethanolic potassium hydroxide (100 ml.) for 1 hr., it gave 2β : 3β-*epoxylanost-8-ene* (1·3 g.), needles (from ethanol), m. p. 136—137°, $[\alpha]_D$ +112° (*c* 1·88), +111° (*c* 1·01), no ultraviolet absorption between 230 and 280 mμ, infrared band at 839 cm.$^{-1}$ (epoxide), no carbonyl band (Found: C, 84·5; H, 11·6. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). This epoxide (500 mg.) in chloroform (25 ml.) was shaken vigorously with aqueous hydrobromic acid (10 ml.; 48% w/w) for 10 min. at room temperature. Crystallisation from methylene dichloride–methanol gave 2α-bromolanost-8-en-3β-ol (410 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +25° (*c* 1·19)}, and infrared spectrum.

Reduction of 2β : 3β-epoxylanost-8-ene (800 mg.) with lithium aluminium hydride (800 mg.) in anhydrous tetrahydrofuran (100 ml.) for 7½ hr. gave lanost-8-en-3β-ol (600 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +57° (*c* 0·88)} and by the conversion into the acetate, also identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +59° (*c* 0·61)}.

2α-Bromolanost-8-en-3β-ol (90 mg.) was refluxed in benzene–methanol (1 : 2; 30 ml.) with " AnalaR " zinc dust (500 mg.; added in three portions) for 3 hr. Crystallisation from methylene dichloride–methanol afforded lanost-8-en-3β-ol (60 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +58° (*c* 0·59)} and by conversion into the acetate, also identified by m. p. and mixed m. p.

Oxidation of 2α-bromolanost-8-en-3β-ol (200 mg.) in benzene–acetic acid (2 : 3; 25 ml.) with Kiliani chromic acid mixture (2·0 ml.) for 30 min. at room temperature gave back 2α-bromolanost-8-en-3-one. The identity of the latter was confirmed by debromination with zinc dust in acetic acid (see above) to lanost-8-en-3-one.

2β-*Bromolanost-8-en-3β-ol and its Derivatives.*—2β-Bromolanost-8-en-3-one (500 mg.) in benzene–methanol (2 : 3; 50 ml.) was treated with sodium borohydride (200 mg.) for 1 hr. Recrystallised with difficulty from light petroleum (b. p. 60—80°) the product (450 mg.; m. p. 163°) gave 2β-*bromolanost-8-en-3β-ol*, soft needles, m. p. 163°, $[\alpha]_D$ +75° (*c* 1·70), max. at 3620 and 1042 cm.$^{-1}$ (equatorial OH) (Found: C, 71·1; H, 10·2; Br, 15·5. $C_{30}H_{51}OBr$ requires C, 71·0; H, 10·1; Br, 15·7%). The derived *acetate* (prepared by pyridine–acetic anhydride overnight at room temperature) formed needles (from methylene dichloride–methanol), m. p. 146—147°, $[\alpha]_D$ +87° (*c* 0·61), max. at 1744 and 1234 cm.$^{-1}$ (acetate) (Found: C, 69·4; H, 9·7. $C_{32}H_{53}O_2Br$ requires C, 69·9; H, 9·7%).

2β-Bromolanost-8-en-3β-ol (150 mg.) in absolute ethanol (25 ml.) was refluxed with potassium hydroxide (700 mg.) for 2½ hr. The crude product, filtered in light petroleum–benzene (1 : 1; 100 ml.) through alumina and crystallised from absolute ethanol, afforded lanost-8-en-3-one (100 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +78° (*c* 0·95)}.

2β-Bromolanost-8-en-3β-ol (90 mg.) in glacial acetic acid (20 ml.) was treated under reflux with " AnalaR " zinc dust (500 mg.) for 1 hr. Crystallisation of the product from methylene

dichloride–methanol furnished lanost-8-en-3β-ol (65 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +58° (*c* 0·65)}.

Lanosta-1 : 8-*dien*-3-*one*.—The total monobromination product of lanost-8-en-3-one (2·1 g.) in redistilled collidine (8 ml.) was heated under reflux for 4 hr. Working up in the usual way, filtration in benzene through alumina, and crystallisation from absolute methanol gave *lanosta*-1 : 8-*dien*-3-*one*, blades, m. p. 109—110°, $[\alpha]_D$ +46° (*c* 1·59), $\lambda_{max.}$ 225 mμ (log ε 3·91) (Found : C, 84·2; H, 11·0. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles (from methylene dichloride–methanol), m. p. 189—190°, $\lambda_{max.}$ 385 mμ (log ε 4·51 in $CHCl_3$) (Found : C, 71·1; H, 8·6; N, 9·8. $C_{36}H_{52}O_4N_4$ requires C, 71·5; H, 8·7; N, 9·3%). Lanosta-1 : 8-dien-3-one was also obtained by the same procedure from pure 2α-bromolanost-8-en-3-one.

2α-*Iodolanost*-8-*en*-3-*one*.—(a) *From* 2α-*bromolanost*-8-*en*-3-*one*. The bromo-ketone (300 mg.) in acetone (20 ml.) was heated under reflux for 3 hr. with sodium iodide in the same solvent (30 ml.; 10% w/v). Working up in the usual way, filtration in benzene solution through alumina, and crystallisation from acetone–methanol gave 2α-*iodolanost*-8-*en*-3-*one* (100 mg.), needles, m. p. 134—135° (decomp.), $[\alpha]_D$ +6° (*c* 1·12), $\lambda_{max.}$ 252 mμ (log ε 2·88), max. at 1721 $cm.^{-1}$ (ketone) (Found : C, 65·1; H, 8·8; I, 22·9. $C_{30}H_{49}OI$ requires C, 65·2; H, 8·9; I, 23·0%).

(b) *From* 2β-*bromolanost*-8-*en*-3-*one*. This bromo-ketone (400 mg.) was treated as above, to give the same iodo-ketone (180 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +5° (*c* 1·08)}, and ultraviolet absorption (Found : C, 65·3; H, 8·6; I, 22·9%).

(c) *From the total monobromination product of lanost*-8-*en*-3-*one*. This material gave the same results as under (*a*) and (*b*).

Lanost-2-*en*-3-*yl Acetate*.—Lanostan-3-one (1·1 g.) in warm *iso*propenyl acetate (30 ml.) was treated with two drops of concentrated sulphuric acid and kept at 100° for 3 hr. Working up in the usual way, filtration in light petroleum–benzene (4 : 1) through alumina, and crystallisation from methylene dichloride–methanol gave *lanost*-2-*en*-3-*yl acetate* (850 mg.), needles, m. p. 130—131°, $[\alpha]_D$ +56° (*c* 2·04) (Found : C, 81·3; H, 11·3. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%).

2 : 2-*Dibromolanostan*-3-*one*.—Lanostan-3-one (500 mg.) in " AnalaR " acetic acid (20 ml.) was treated at 16° with bromine (2·05 mols.) in the same solvent (25 ml.) for 10 min. and then left at room temperature for 6 hr. The crystalline product was filtered off and identified as 2 : 2-*dibromolanostan*-3-*one* (450 mg.), needles, m. p. 135—136°, $[\alpha]_D$ +29° (*c* 3·22), max. at 1716 $cm.^{-1}$ (ketone) (Found : C, 61·4; H, 8·6; Br, 27·4. $C_{30}H_{50}OBr_2$ requires C, 61·4; H, 8·6; Br, 27·3%).

2α-*Bromolanostan*-3-*one*.—(a) *From lanost*-2-*en*-3-*yl acetate*. The enol acetate (450 mg.) in " AnalaR " acetic acid (25 ml.) was treated with bromine (1·1 mols.) in the same solvent (5 ml.) at room temperature for 20 min. Crystallisation from ethanol gave 2α-*bromolanostan*-3-*one* (300 mg.), needles, m. p. 123—124°, $[\alpha]_D$ +34° (*c* 2·22), $\lambda_{max.}$ 289 mμ (log ε 1·59) (Found : C, 71·0; H, 10·4; Br, 15·5. $C_{30}H_{51}OBr$ requires C, 71·0; H, 10·1; Br, 15·7%).

(b) *From lanostan*-3-*one*. The ketone (740 mg.) was treated with bromine as above, to give the same bromo-ketone (670 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +34° (*c* 1·13), +34° (*c* 1·07)}.

Treatment of 2α-bromolanostan-3-one (300 mg.) in glacial acetic acid (10 ml.) under reflux with " AnalaR " zinc dust (1·0 g.) for 2 hr. furnished lanostan-3-one (200 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +24° (*c* 1·67)}.

2α-*Bromolanostan*-3β-*ol and its Derivatives*.—2α-Bromolanostan-3-one (1·0 g.) in benzene–absolute methanol (1 : 2; 30 ml.) was treated with sodium borohydride (400 mg.) for 1 hr. at room temperature. Filtration gave 2α-*bromolanostan*-3β-*ol* (760 mg.), needles (from methylene dichloride–methanol), m. p. 168—169°, $[\alpha]_D$ +23° (*c* 1·75), max. at 3620 and 1055 $cm.^{-1}$ (equatorial OH) (Found : C, 71·3; H, 10·4; Br, 14·5. $C_{30}H_{53}OBr$ requires C, 70·7; H, 10·5; Br, 15·7%). The derived *acetate* (prepared by pyridine–acetic anhydride overnight at room temperature) formed platelets (from methylene dichloride–methanol), m. p. 154—155°, $[\alpha]_D$ +26° (*c* 1·40), bands at 1746 and 1230 $cm.^{-1}$ (acetate) (Found : C, 69·3; H, 9·9; Br, 14·8. $C_{32}H_{55}O_2Br$ requires C, 69·7; H, 10·0; Br, 14·5%).

2α-Bromolanostan-3β-ol (100 mg.) was refluxed in glacial acetic acid (20 ml.) with " AnalaR " zinc dust for 2 hr. Isolation of the product in the usual way furnished lanostan-3β-ol (75 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +36° (*c* 0·79)}.

2α-Bromolanostan-3β-ol (1·0 g.) was refluxed in 5% absolute-ethanolic potassium hydroxide (80 ml.) for 1 hr. Isolation in the usual way gave 2β : 3β-*epoxylanostane* (700 mg.), needles

(from ethanol), m. p. 170—171°, $[\alpha]_D$ +64° (*c* 1·29), max. at 841 cm.$^{-1}$ (epoxide), no carbonyl absorption (Found: C, 84·4; H, 12·0. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%).

Treatment of this oxide (120 mg.) in chloroform (12 ml.) with 48% aqueous hydrobromic acid (2·0 ml.) at room temperature for 10 min. (vigorous shaking) gave back 2α-bromolanostan-3β-ol (115 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +23° (*c* 1·05)}, and infrared spectrum.

Reduction of 2β : 3β-epoxylanostane (300 mg.) in refluxing anhydrous tetrahydrofuran (30 ml.) with lithium aluminium hydride for 7 hr. afforded lanostan-3β-ol (220 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +35° (*c* 0·95)}. The identity was confirmed by acetylation to lanostanyl acetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +40° (*c* 0·52)}.

Lanost-2-ene.—Lanostanol (8·0 g.) in dry pyridine (60 ml.) and benzoyl chloride (20 ml.) was kept at 100° for 1½ hr. Crystallisation of the product from benzene–methanol furnished *lanostan-3β-yl benzoate* (6·5 g.), needles, m. p. 204—205°, $[\alpha]_D$ +54° (*c* 1·39) (Found: C, 83·3; H, 10·6. $C_{37}H_{58}O_2$ requires C, 83·1; H, 10·9%). This benzoate (1·0 g.) was heated under reflux at atmospheric pressure for 2 hr. The product was chromatographed over alumina in light petroleum, to give lanost-2-ene (380 mg.), needles (from acetone), m. p. 100—101°, $[\alpha]_D$ +62° (*c* 0·38) (Found: C, 87·3; H, 12·6. $C_{30}H_{52}$ requires C, 87·3; H, 12·5%).

Lanost-2-ene was more conveniently prepared by the following procedure. Lanostan-3β-ol (3·5 g.) in anhydrous pyridine (40 ml.) and redistilled phosphorus oxychloride (5·0 ml.) was kept at 100° for 1½ hr. with good stirring. Working up in the usual way, filtration through alumina in light petroleum, and slow crystallisation from ethanol afforded an impure lanost-2-ene (2·4 g.), m. p. 80—82°, $[\alpha]_D$ +51° (*c* 1·10) (Found: C, 87·3; H, 12·5%). This was characterised as a mixture of lanost-2-ene and 3-*iso*propylidene-A-norlanostane in the following way. Hydrogenation of the hydrocarbon (110 mg.) in glacial acetic acid (15·0 ml.) at 85—90° for 1 hr. over platinum gave lanostane (75 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +35° (*c* 0·75)}. In contrast, hydrogenation of pure lanost-2-ene (see above) (50 mg.) under the same conditions gave, without difficulty, lanostane, identified in the same way, in essentially quantitative yield (49 mg.). Treatment of crude lanost-2-ene (500 mg.) in ether (5·0 ml.) at 20° with bromine (6·7 ml. of a solution of 0·5 ml. of bromine in 50 ml. of glacial acetic acid) overnight at room temperature gave, after filtration through alumina in light petroleum, pure lanost-2-ene (100 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +59° (*c* 0·80)}. Treatment with chlorine gave the same result. Ozonolysis of crude lanost-2-ene (600 mg.) in ethyl acetate (50 ml.) at −20° for 3 hr. gave, on addition of water and distillation, acetone, isolated as its 2 : 4-dinitrophenylhydrazone (43 mg.) and identified by m. p. and mixed m. p. A specimen of 3-*iso*propylidene-A-norlanostane prepared for comparative purposes had m. p. 116—117°, $[\alpha]_D$ +38° (*c* 2·47). Barton, Ives, and Thomas [13] give m. p. 110—112°, $[\alpha]_D$ +33°.

Pure lanost-2-ene was also obtained in the following way. 2α-Bromolanostan-3β-yl acetate (150 mg.) was refluxed in benzene–methanol (1 : 1; 30 ml.) with " AnalaR " zinc dust (500 mg.; added portionwise) for 1 hr. Crystallisation from acetone afforded lanost-2-ene (100 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +58° (*c* 1·02)}.

2α : 3α-*Epoxylanostane and its Derivatives.*—Lanost-2-ene (1·0 g.) in chloroform (20 ml.) was kept with excess of perbenzoic acid at 0° for 48 hr. Working up in the usual way and crystallisation from acetone gave 2α : 3α-epoxylanostane (750 mg.), needles, m. p. 124—125°, $[\alpha]_D$ +34° (*c* 0·91), max. at 828 cm.$^{-1}$ (epoxide), no carbonyl absorption (Found: C, 84·2; H, 12·1. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). This oxide was also obtained from crude lanost-2-ene (see above) in the same way.

Reduction of the oxide (500 mg.) under reflux in anhydrous tetrahydrofuran (40 ml.) with lithium aluminium hydride (500 mg.) gave *lanostan-3α-ol*, needles (from methylene dichloride–methanol), m. p. 163—164°, $[\alpha]_D$ +19° (*c* 0·65) (Found: C, 83·3; H, 12·3. $C_{30}H_{54}O$ requires C, 84·0; H, 12·2%). Treatment with pyridine–acetic anhydride overnight at room temperature gave the *acetate*, platelets (from methylene dichloride–methanol), m. p. 152—153°, $[\alpha]_D$ −5° (*c* 0·69), max. at 1741 and 1244 cm.$^{-1}$ (acetate) (Found: C, 80·8; H, 11·6. $C_{32}H_{56}O_2$ requires C, 81·3; H, 11·9%). Oxidation of this alcohol (100 mg.) in benzene–acetic acid (1 : 3; 40 ml.) with Kiliani chromic acid mixture (1·0 ml.) at room temperature for 25 min. afforded lanostan-3-one (70 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +22° (*c* 0·57)}, and reduction with sodium borohydride to lanostan-3β-ol (m. p. and mixed m. p.).

[13] Barton, Ives, and Thomas, *J.*, 1954, 903.

2β-*Bromolanostan*-3α-*ol and its Derivatives*.—2α : 3α-Epoxylanostane (200 mg.) was treated with hydrobromic acid as in the examples given above. Crystallisation of the product from acetone–methanol furnished 2β-*bromolanostan*-3α-*ol* (200 mg.), needles, m. p. 110°, then 131° (after resolidification), $[\alpha]_D$ +77° (*c* 0·72), +76° (*c* 0·79), max. at 3620 and 992 cm.$^{-1}$ (axial OH) (Found : C, 70·8; H, 10·4; Br, 15·4. $C_{30}H_{53}OBr$ requires C, 70·7; H, 10·5; Br, 15·7%).

2β-Bromolanostan-3α-ol (100 mg.) was refluxed with N-ethanolic potassium hydroxide (10 ml.) for 1 hr., to give 2α : 3α-epoxylanostane, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +33° (*c* 0·47)}.

2β-Bromolanostan-3α-ol (700 mg.) in benzene–acetic acid (1 : 1; 60 ml.) was oxidised with Kiliani chromic acid mixture (6·0 ml.) during 30 min. at room temperature. Working up in the usual way gave 2β-*bromolanostan*-3-*one* (450 mg.), cubes (from ethanol), m. p. 154—155°, $[\alpha]_D$ +121° (*c* 0·66), +128° (*c* 0·58), $\lambda_{max.}$ 285 mμ (log ε 1·88) (Found : C, 71·0; H, 9·9; Br, 15·45. $C_{30}H_{51}OBr$ requires C, 71·0; H, 10·1; Br, 15·75%).

Equilibration of 2α- *and* 2β-*Bromolanostan*-3-*one*.—A solution of the bromo-ketone (60—80 mg.) in chloroform (10 ml.) was treated with hydrogen bromide in acetic acid (1·0 ml.; *d*, 1·5) in a 2 dm. polarimeter tube. The rotation of the 2α-bromo-ketone did not change at all; that of the 2β-bromo-ketone dropped to $[\alpha]_D$ +34° in 90 min. and remained thereafter unchanged. In both experiments the product was shown to be 2α-bromolanostan-3-one by m. p. and mixed m. p.

2β-*Bromolanostan*-3β-*ol*.—2β-Bromolanostan-3-one (200 mg.) in benzene–methanol (1 : 1; 10 ml.) was reduced with sodium borohydride (60 mg.) at room temperature for 30 min. Crystallisation of the product from methylene dichloride–methanol gave 2β-*bromolanostan*-3β-*ol* (200 mg.), needles, m. p. 172—173° (decomp.), $[\alpha]_D$ +21° (*c* 1·46), max. at 3550 and 1056 cm.$^{-1}$ (equatorial OH) (Found : C, 70·6; H, 10·5; Br, 15·6. $C_{30}H_{53}OBr$ requires C, 70·7; H, 10·5; Br, 15·7%). Acetylation in the usual way (see above) furnished the derived *acetate*, platelets (from methylene dichloride–methanol), m. p. 177—178°, $[\alpha]_D$ +66° (*c* 0·32), max. at 1740 and 1234 (acetate) (Found : C, 69·7; H, 9·8; Br, 14·9. $C_{32}H_{55}O_2Br$ requires C, 69·7; H, 10·0; Br, 14·5%).

2β-Bromolanostan-3β-ol (100 mg.) was refluxed with N-ethanolic potassium hydroxide (10 ml.) for 1 hr. Crystallisation of the product from acetone–methanol furnished lanostan-3-one (50 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +24° (*c* 0·47)}.

2α-*Iodolanostan*-3-*one*.—2α-Bromolanostan-3-one (400 mg.) in " AnalaR " acetone (10 ml.) was refluxed with sodium iodide (4·0 g.) in the same solvent (60 ml.) for 3 hr. The product, filtered through alumina in benzene solution and crystallised from acetone–methanol, afforded 2α-*iodolanostan*-3-*one* (300 mg.), needles, m. p. 124—125° (decomp.), $[\alpha]_D$ +7° (*c* 1·03), $\lambda_{max.}$ 261 mμ (log ε 2·78), infrared max. at 1717 cm.$^{-1}$ (ketone) (Found : C, 65·3; H, 8·8; I, 22·6. $C_{30}H_{51}OI$ requires C, 65·0; H, 9·2; I, 23·0%).

Lanost-1-*en*-3-*one*.—2α-Bromolanostan-3-one (800 mg.) in redistilled collidine (7·0 ml.) was refluxed for 4 hr. The product, filtered through alumina in light petroleum–benzene (1 : 1) and crystallised from acetone–methanol, furnished *lanost*-1-*en*-3-*one* (150 mg.), blades, m. p. 118—119°, $[\alpha]_D$ +48° (*c* 1·17), $\lambda_{max.}$ 230 mμ (log ε 3·81) (Found : C, 84·7; H, 11·8. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). The 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way, formed needles (from methylene dichloride–methanol), m. p. 217—218°, $\lambda_{max.}$ 384 mμ (log ε 4·12) (Found : C, 71·1; H, 9·1; N, 9·2. $C_{36}H_{54}O_4N_4$ requires C, 71·25; H, 9·0; N, 9·2%).

Rates of Dehydrohalogenation of Halogenohydrins (with Drs. J. C. Banerji and R. C. Cookson).—The following conditions were employed. The halogenohydrin (1 mmole) in 350 ml. of dioxan–water (50 : 16 v/v) was mixed with N-aqueous sodium hydroxide (3·0 ml.) at 25° and held at this temperature. Aliquot portions were removed periodically for titration with standard acid. The data obtained are summarised in the Table. At the end of the reaction the products from the steroid halogenohydrins were worked up in the usual way and characterised (by m. p., mixed m. p., and rotation) as follows : 2α-chloro- and 2α-bromo-cholestan-3β-ol (2β : 3β-epoxycholestane), 2β-chloro- and 2β-bromo-cholestan-3α-ol (2α : 3α-epoxycholestane), 2α-chloro- and 3α-bromo-cholestan-2β-ol (2β : 3β-epoxycholestane).

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The University, Glasgow, W.2.
Chelsea Polytechnic, London, S.W.3.

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